A systematic review on imaging and diagnostic modalities for the detection, evaluation, and surgical planning of upper and lower extremity lymphedema

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ABSTRACT

Objective: The purpose of this systematic review was to evaluate imaging and diagnostic modalities for their roles in (1) diagnosing upper and lower extremity lymphedema, (2) detecting subclinical disease through prospective surveillance, (3) providing anatomical assessment of the lymphatic system, and (4) guiding surgical treatment planning.

Methods: A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The search included PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus from January 2010 to April 2026. Four reviewers screened 2847 articles using Covidence software. The inclusion criteria were studies that reported original data on one or more imaging modalities and presented diagnostic accuracy, reliability, staging parameters, or impact on surgical planning.

Results: A total of 28 studies were included, comprising four randomized controlled trials, 12 prospective diagnostic studies, six cohort studies, one observational study, and five systematic reviews or meta-analyses. In upper extremity studies, predominantly composed of breast cancer-related lymphedema (BCRL), bioimpedance spectroscopy (BIS) demonstrated a sensitivity of up to 100% and a specificity of 98% for early detection, with the PREVENT trial showing a 59% relative risk reduction in chronic BCRL through BIS-triggered surveillance. Indocyanine green (ICG) lymphography achieved 100% diagnostic accuracy vs 62% for lymphoscintigraphy in early disease, and ultra-high-frequency ultrasound imaging at 70 MHz achieved 94.9% sensitivity for vessel detection. In the lower extremity, magnetic resonance lymphangiography (MRL) at 3.0 T achieved 100% sensitivity for lymph vessel abnormalities vs 79% for lymphoscintigraphy ($\kappa = 0.93$ for delayed drainage). Ultrasound imaging achieved 95.5% sensitivity and 92.9% specificity for vessel detection. Two validated ICG-based classifications, saphenous calf thigh and Shinaoka, enabled lower extremity-specific severity staging.

Conclusions: This systematic review identified important differences in the evidence supporting imaging and diagnostic modalities across the four clinical domains evaluated. For diagnosis and subclinical detection, BIS-triggered prospective surveillance for upper extremity lymphedema is supported by randomized controlled trial evidence demonstrating significant reduction in chronic BCRL progression. However, comparable trial data for the lower extremity remains absent. For anatomical assessment, region-specific ICG classification systems (saphenous calf thigh and Shinaoka) address the unique drainage patterns of the lower extremity, while MRL provides comprehensive deep and superficial system visualization across both regions. For surgical planning, the combined use of near-infrared fluorescence lymphangiography and MRL offers complementary information to guide microsurgical interventions. (J Vasc Surg Venous Lymphat Disord 2026;■:102592.)

Keywords: Lymphedema; Imaging; Bioimpedance spectroscopy; Indocyanine green lymphography; Magnetic resonance lymphangiography

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Additional material for this article may be found online at www.jvsvenous.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal Policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2026.102592

Lymphedema is a clinical manifestation of lymphatic system insufficiency characterized by the accumulation of protein-rich fluid in the interstitial space.[1] According to the International Society of Lymphology (ISL) 2020 Consensus Document, the condition is classified as either primary (congenital or hereditary) due to lymphatic dysplasia or secondary (acquired) resulting from damage or obstruction of a previously intact lymphatic system.[2]

Upper extremity lymphedema, predominantly breast cancer-related lymphedema (BCRL), accounts for most cases in industrialized nations and affects approximately 20% of women after axillary lymph node dissection and radiation therapy.[3-6] Lower extremity lymphedema presents unique diagnostic and therapeutic challenges with more diverse etiologies, including primary lymphedema, gynecological cancer treatment, melanoma treatment, and venous insufficiency-related secondary lymphedema.[7]

Accurate, stage-specific imaging is required to confirm the diagnosis, detect subclinical disease for prospective surveillance models, and guide microsurgical reconstruction.[8] As a chronic and progressive condition, lymphedema imposes significant physical, psychological, and financial burdens on patients, leading to pain, recurrent infections, functional impairment, and diminished quality of life.[8,9]

The purpose of this systematic review is to separately analyze the evidence for imaging and diagnostic modalities used in upper vs lower extremity lymphedema across four clinical domains: (1) diagnostic accuracy, (2) subclinical detection through prospective surveillance, (3) anatomical assessment of the lymphatic system, and (4) surgical treatment planning. By evaluating the evidence across these domains for each anatomical region, this review aims to equip clinicians with the knowledge to select the most appropriate diagnostic tools for early detection and to guide surgical planning.

METHODS

Protocol and registration. The protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and is available from the corresponding author upon request.[10] This systematic review was conducted with the assistance of an expert librarian and was not prospectively registered in PROSPERO.

Eligibility criteria. Studies were eligible if they included adults aged 18 years or older with clinically diagnosed primary or secondary limb lymphedema, reported original data on one or more imaging modalities including lymphoscintigraphy (LSG), near-infrared fluorescence lymphangiography/indocyanine green (NIRF-L/ICG), magnetic resonance lymphangiography/magnetic resonance imaging (MRL/MRI), ultrasound (US) imaging, computed tomography (CT), single-photon emission computed tomography/CT (SPECT/CT), photoacoustic imaging, or bioimpedance spectroscopy (BIS), and presented findings relevant to one or more of the following: diagnostic accuracy (sensitivity, specificity, and area under the curve [AUC]), anatomical lymphatic vessel or node identification, severity staging or classification, impact on surgical planning, or effectiveness in prospective surveillance and early detection programs. Eligible study designs included prospective or retrospective cohorts, cross-sectional studies, randomized controlled trials (RCTs), and systematic reviews or meta-analyses published in English. Exclusion criteria comprised case reports and case series with fewer than five participants, animal studies, conference abstracts without full-text availability, studies not published in English, and pediatric populations younger than 18 years.

Although BIS is a pathophysiological assessment tool that measures tissue fluid accumulation through bioelectrical impedance rather than producing anatomical images, it was included in this review because it serves as a primary diagnostic and surveillance tool for lymphedema detection. In addition, it is integral to current clinical protocols that guide subsequent imaging and treatment decisions. BIS is included alongside traditional imaging modalities to provide a comprehensive assessment of all available diagnostic technologies used in lymphedema evaluation.

Information sources and search strategy. Five electronic databases were searched from January 1, 2010, to August 1, 2025, and an updated search in April 2026. The search was limited to publications from January 1, 2010, onward for two reasons: (1) major advances in lymphedema imaging technology, including Food and Drug Administration clearance of the lymphedema index (L-Dex) bioimpedance spectroscopy device (2008), widespread adoption of ICG lymphography, and development of dedicated MRL protocols, occurred predominantly after 2008 to 2010; and (2) the ISL published updated consensus documents during this period that redefined staging criteria, making pre-2010 studies less comparable to current diagnostic frameworks. An updated search was performed in April 2026 to capture any additional relevant studies published ensuring that the most current evidence was included. The databases searched included: PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus. Search concepts combined "lymphedema," "lymphography," "imaging," and individual modalities such as "lymphoscintigraphy," "magnetic resonance," "indocyanine green," "ultrasound," "photoacoustic," and "bioimpedance spectroscopy." Complete search strategies are provided in the Appendix.

Selection process. After duplicate removal using Covidence systematic review software, four reviewers independently screened titles and abstracts, followed by

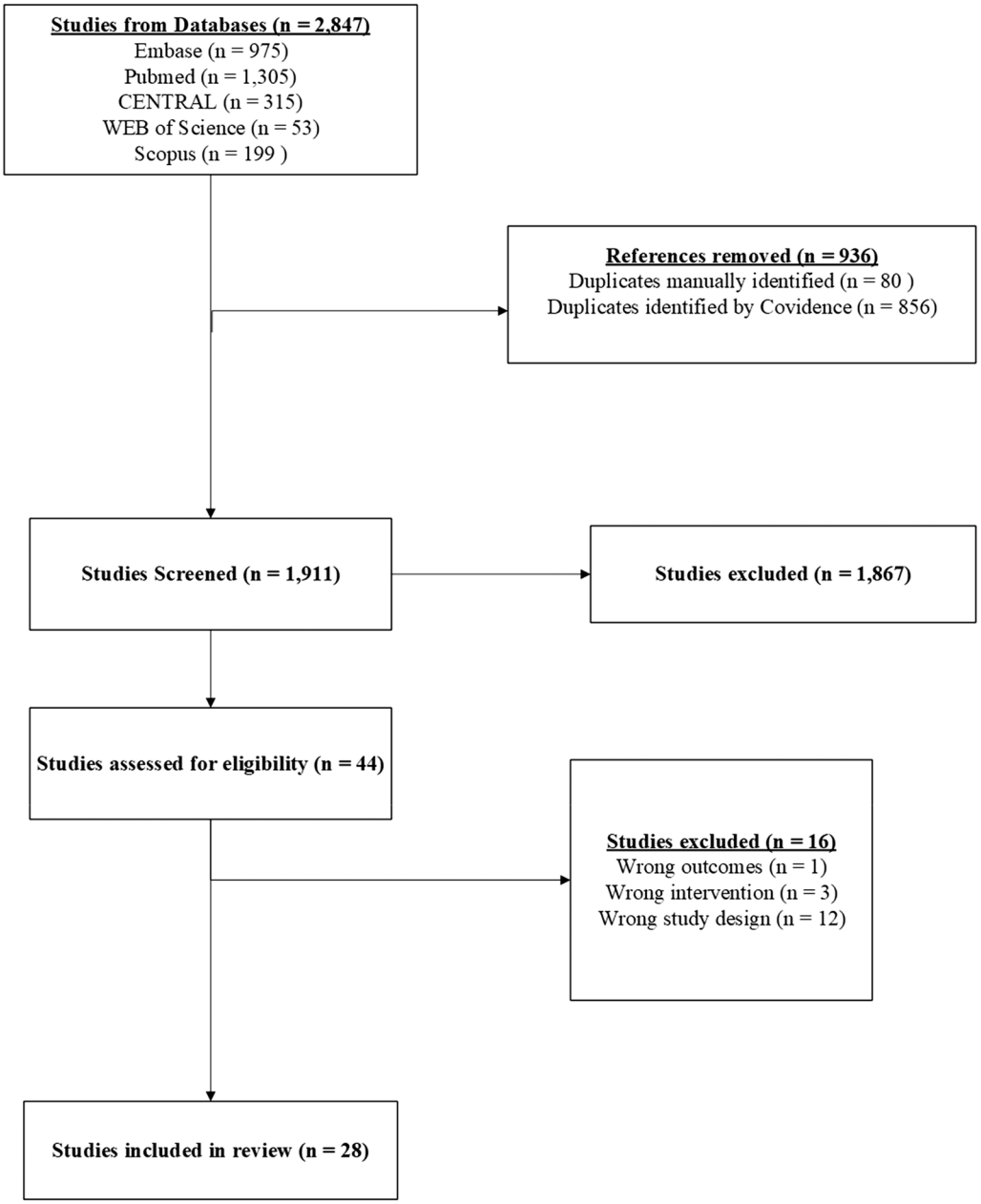

Fig. Flow diagram illustrating the study selection process following PRISMA 2020 guidelines. A total of 2847 records were identified through searches of five electronic databases: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. After the removal of 936 duplicates using Covidence systematic review software, 1911 unique records remained for screening. Title and abstract screening by four independent reviewers resulted in the exclusion of 1867 records that did not meet the eligibility criteria. Forty-four full-text articles were assessed for eligibility, of which 16 were excluded. Twenty-eight studies met all inclusion criteria and were included in the final synthesis. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

independent full-text review of potentially eligible records. Inter-rater reliability was ensured through calibration exercises before screening. Disagreements at each stage were resolved by consensus with all reviewers.

Data collection process. Using a standardized data extraction form, four reviewers independently abstracted study design, sample size, gender distribution, limb involved (upper vs lower extremity), type of lymphedema (primary vs secondary), imaging protocol, reference standard, and main quantitative outcomes including sensitivity, specificity, confidence intervals (CIs), likelihood ratios, AUC, and predictive values. Discrepancies were resolved by discussion and consensus.

Table I. Characteristics of all included primary studies

Study	Year	Country	N	Lymphedema type	Modality	Follow-up duration	Reference diagnostic standard	Main diagnostic values	Classification criteria
Upper extremity studies									
Diagnostic accuracy studies									
Fu et al[11]	2013	USA	141	Secondary	BIS (L-Dex)	Cross-sectional (single time point)	Clinical diagnosis with circumferential tape measurement (≥200 mL volume difference)	Sensitivity 80% (95% CI, 0.66-0.89); specificity 90% (95% CI, 0.84-0.94); AUC = 0.86	L-Dex >7.1 (absolute diagnosis without baseline); L-Dex change >6.5 from baseline (surveillance trigger)
Ward et al[12]	1992	Australia	30	Secondary	MFBIA	Cross-sectional (single time point)	Clinical diagnosis with limb volume measurement	Quantitative agreement with clinical diagnosis of lymphedema and with circumferential limb volume measurements; demonstrated MFBIA can distinguish extracellular fluid accumulation from other causes of limb volume change (specific Se/Sp and ICC not reported)	Impedance ratio comparison between affected and unaffected limbs at multiple frequencies; extracellular fluid volume estimation; no formal classification threshold proposed; established foundational evidence for BIS in lymphedema assessment
Cornish et al[13]	2001	Australia	102 patients, 60 healthy controls	Secondary	MFBIA	24 months (prospective monitoring with measurements presurgery, 1 month postsurgery, then at 2-month intervals)	Clinical diagnosis with circumferential limb volume measurements; MFBIA ratio exceeding 3 standard deviations from pre-surgery baseline confirmed by clinical examination	Sensitivity 100%; specificity 98%; MFBIA detected lymphedema up to 10 months before clinical diagnosis; circumferential measurement sensitivity only 5% for early detection; at the time of MFBIA detection, only 1 of 20 patients with lymphedema had a positive circumferential volume test	MFBIA extracellular fluid volume ratio (affected/unaffected limb) exceeding 3 standard deviations (>0.102) from pre-surgery baseline deemed predictive of lymphedema onset; positive result confirmed by repeat measurement 1 week later followed by clinical referral
Mihara et al[14]	2012	Japan	32	Secondary	ICG, LSG	Cross-sectional (single time point)	Clinical diagnosis (ISL staging) with lymphoscintigraphy as comparator	ICG: 100% diagnostic accuracy; LSG: 62% sensitivity	ICG dermal backflow patterns (linear, splash, stardust, diffuse) per Yamamoto classification
Bae et al[15]	2018	South Korea	22	Secondary	MRL, LSG	Cross-sectional (single time point)	Lymphoscintigraphy as comparator; clinical diagnosis	MRL: sensitivity 92%-100%, specificity 85%-100%	Abnormal lymphatic vessel morphology and asymmetric enhancement on MRL
Surveillance and early detection studies									
Ridner et al[16]	2022	USA/ Australia	879 analyzed (963 randomized; BIS, n = 442, TM, n = 437)	Secondary	BIS (L-Dex U400), TM (circumferential volume)	Median 32.9 months (IQR, 22-35 months)	Progression to chronic BCRL defined as ≥10% arm volume change from presurgical baseline requiring complex decongestive physiotherapy	BIS-triggered intervention at a lower rate than TM (20.1% vs 27.5%, $P = .011$); longer median time to trigger with BIS (9.7 vs 3.9 months, $P = .001$); BIS reduced progression to CDP compared with TM (7.9% vs 19.2%; relative risk = 0.41; 95% CI, 0.13-0.81; absolute reduction 11.3%; 95% CI, 2.3-20.3; $P = .016$); 59% relative reduction in progression	L-Dex change ≥6.5 from presurgical baseline triggers early compression intervention (class 2 sleeve and gauntlet, 23-32 mm Hg, 12 hours/d for 4 weeks); TM trigger: at-risk arm volume change ≥5% and <10% from baseline; progression in both groups defined as TM volume change ≥10% from presurgical baseline requiring CDP referral

Table I. Continued.

Study	Year	Country	N	Lymphedema type	Modality	Follow-up duration	Reference diagnostic standard	Main diagnostic values	Classification criteria
Stout et al[17]	2012	USA	100	Secondary	Prospective surveillance model vs traditional impairment-based model	1-year cost analysis	Medicare 2009 physician fee schedule; CPT codes for physical therapy; averaged durable medical equipment costs from 3 U.S.-based distributors and 3 garment manufacturers	PSM cost: $636.19 per patient per year; TM cost: $3124.92 per patient per year; per 100 patients: PSM $38,272.83 vs TM $104,684.82; sensitivity analysis showed PSM less costly at nearly every incidence rate (10%-48%); 80.5% of early-stage cases would have to progress to an advanced stage before PSM cost exceeds TM	Early-stage lymphedema: stage 0 or I, amenable to conservative treatment (compression garment intervention); advanced-stage lymphedema: stage II or higher, visible, palpable, requiring CDT; PSM detects early-stage BCRL through interval surveillance at preoperative, 1, 3, 6, 9, and 12 months postsurgery; >3%-5% volume increase triggers ready-made compression sleeve and gauntlet
Surgical planning studies									
Wiser et al[18]	2020	USA	118	Secondary	ICG, BIS (L-Dex), LSG, MRA, limb volume, PROMs (LLIS, ULL-27)	Cross-sectional (single time point)	Limb volume difference >10% by perometer as diagnostic threshold	ICG: 100% sensitivity (all affected limbs demonstrated pathological patterns); L-Dex >10: sensitivity 91.2%, specificity 77.5%, PPV 87.3%; LSG: sensitivity 88%, specificity 41.4%, PPV 72.1%; MRA fluid accumulation: sensitivity 94.2%, specificity 44%; MRA fat hypertrophy: sensitivity 96.2%, specificity 64%; circumference difference >2 cm: sensitivity 82.8%, specificity 85.3%, PPV 74.4%	ICG dermal backflow patterns per Yamamoto classification (linear, splash, stardust, diffuse); L-Dex score >10 diagnostic for lymphedema; ISL staging (0-3); limb volume difference >10% by perometer; MRA assessment of fluid accumulation, fat hypertrophy, and axillary venous stenosis
Treatment response assessment studies									
Gothard et al[19]	2010	UK	58	Secondary	Perometry, LSG, dielectric constant meter	12 months	Perometry: ipsilateral limb volume expressed as percentage of contralateral limb volume; lymphoscintigraphy: fractional removal rate constant (k) of radioisotopic tracer (% min^{-1}); dielectric constant: dimensionless measure proportional to extracellular water content	Primary end point: no significant difference in volume change between HBO and control (median change, −2.9% vs −0.3%; $P = .93$); response rate (≥8% volume reduction): 30% HBO vs 18.8% control (RR = 1.60; 95% CI, 0.50-5.09; $P = .50$); lymphoscintigraphy: no significant differences in clearance rates between groups; dielectric constant: possible greater reduction in upper arm extracellular water in HBO group but not statistically significant	Lymphedema defined as ≥15% increase in ipsilateral arm volume compared with contralateral arm; response defined as ≥8% absolute reduction in ipsilateral arm volume relative to contralateral at 12 months; HBO protocol: 100% oxygen at 2.4 atmospheres absolute for 100 minutes, 30 sessions over 6 weeks

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Table I. Continued.

Study	Year	Country	N	Lymphedema type	Modality	Follow-up duration	Reference diagnostic standard	Main diagnostic values	Classification criteria
Bok et al[20]	2018	South Korea	45	Secondary	Acoustic radiation force impulse (ARFI) imaging, Conventional B-mode ultrasonography for subcutaneous	Immediately before and after a single 30-minute IPC session	Lymphedema diagnosed by circumference difference >2 cm between affected and normal arm confirmed by lymphoscintigraphy	Arm circumference significantly decreased in all groups ($P = .01, .00, 0.00$); subcutaneous tissue thickness significantly decreased in all groups ($P = .01, .03, 0.00$) with 35 mm Hg showing significantly greater reduction than other groups ($P = .014$); SWV significantly decreased only in 35 mm Hg group ($P = .02$) with significant between-group difference ($P = .034$); positive correlation between SWV reduction and subcutaneous depth reduction ($r = 0.63$; $P = .00$)	Stage II postmastectomy lymphedema; circumference difference >2 cm between affected and normal arm; lymphoscintigraphy-confirmed lymphatic dysfunction; IPC applied using Lympha Press Plus (Mego Afek, Israel) with 10-chamber sleeve in sequential mode; 30-minute treatment with 18-second inflation and 4-second deflation cycles; measurements taken at 10 cm proximal to antecubital fold midpoint
Barbieux et al[21]	2023	Belgium	52	Secondary	LSG	Short-term (during imaging session)	LSG, radioactivity quantification in lymph nodes and dermal backflow areas; ratio of increased activity (RIA)	MLD increased lymph node activity by 28% vs rest ($P < .0001$); LG-MLD was 19% more efficient than St-MLD in lymph node filling ($P = .0210$); both MLD techniques decreased dermal backflow by 11%; no significant difference between techniques for dermal backflow ($P = .5478$)	Secondary upper limb lymphedema; lymphoscintigraphy protocol approved by Belgian Society of Nuclear Medicine; St-MLD followed Leduc method; LG-MLD adapted based on patient imaging with resorption maneuvers over dermal backflow areas, increased pressure over deep lymphatics, and insistence on lymphatic outlet path
Lower extremity studies									
Diagnostic accuracy studies									
Weiss et al[22]	2015	Germany	34	Primary	Planar LSG and SPECT/CT	Cross-sectional (single time point)	Semiquantitative transport index (TI); TI range, 0-45; TI <10 normal, TI ≥10 pathological	SPECT/CT provided additional information in 96.4% of pathological cases: anatomical allocation (64%), dermal backflow detection (86%), lymph node verification (46%), lymph vessel visualization (4%)	Primary lower limb lymphedema per ISL 2013 classification
Lu et al[23]	2010	China	31 (40 lower extremities)	Primary	Heavily T2-weighted MRI, MRL	Cross-sectional (single time point)	Clinical diagnosis (Foeldi and Foeldi classification)	Heavily T2-weighted MRI detected lymphangiectasia in 97.5% of lower legs vs 90% for MRL; significantly more dilated vessels on T2WI (mean 6.82 vs 4.88; $P = .003$); MRL demonstrated superior SNR (257.33 vs 168.70; $P < .01$), CNR (207.20 vs 134.86; $P < .01$), and image quality scores (3.81 vs 2.92; $P < .01$)	Dilated lymphatic vessel morphology (beaded appearance), maximum vessel diameter, image quality (1-4 scoring scale), accumulated lymph fluid regions, and honeycombing pattern extent on heavily T2-weighted MRI and gadolinium-enhanced MRL

Table I. Continued.

Study	Year	Country	N	Lymphedema type	Modality	Follow-up duration	Reference diagnostic standard	Main diagnostic values	Classification criteria
Lohrmann et al[24]	2009	Germany	26 (LE)	Lipedema and lipo-lymphedema (lower extremities)	MRL	Single imaging session; acquisitions at 15, 25, 35, 45, and 55 min postinjection	Clinical diagnosis of lipedema/lipo-lymphedema; MRL morphological and functional assessment of lymphatic vessels and lymph nodes	100% (16/16) lipo-lymphedema extremities showed epifascial lymphedema; 0% (0/10) pure lipedema extremities showed lymphedema; enlarged lymphatic vessels detected in 6/10 pure lipedema extremities (up to 2 mm) indicating subclinical impairment; dermal backflow in 2/16 lipo-lymphedema extremities	Clinical diagnosis of lipedema or lipo-lymphedema; exclusion: MRI contraindications, renal insufficiency, gadolinium allergy
Suehiro et al[25]	2014	Japan	45	Secondary	B-mode ultrasonography	Single assessment	LAS for lymph transport confirmation; ISL 2009 staging; venous duplex	SEG and SEF correlated with ISL stage; DE showed gravity-dependent distribution; LE showed medial thigh/leg echogenicity in early stages correlating with ventromedial bundle	Secondary lymphedema: impaired lymph transport on LAS, oncologic surgery, no gait disturbance; dependent edema: normal lymph transport on LAS, prolonged sitting, no chronic venous insufficiency signs; both groups: normal venous duplex, systemic causes excluded
Notohamiprodjo et al[26]	2012	Germany	30	Primary and Secondary	MRL compared with LSG	Single assessment	Combined consensus of both techniques and clinical presentation as reference standard; ISL 2003 classification	Delay: both modalities 100% sensitivity/specificity; pattern: MRL 92% sensitivity vs LS 100%; lymph vessels: MRL 100% sensitivity vs LS 79%; lymph nodes: LS 100% specificity vs MRL 78%; κ values: delay 0.93, pattern 0.84, lymph nodes 0.67, levels 0.77, lymph vessels 0.50	ISL stages I-III; drainage delay scored 0-3; drainage pattern scored 0-3; lymph node and vessel depiction scored 0-2; anatomic levels 0-3 (feet to pelvis)
Anatomical assessment and classification studies									
Hara and Mihara[27]	2021	Japan	105	Primary and secondary	Multilymphosome ICG lymphography	Single preoperative assessment	LSG; ISL staging (stages 1, 2a, 2b, 3)	Saphenous lymphosome: 95.5% type 1 (medial); lateral calf: 29.9% type 1; lateral thigh: 16.9% type 1; type 2 percentage increased with lymphoscintigraphic staging progression; lymphatic vessels shifted medial to lateral and disappeared as severity worsened	SCaT classification: lymphatic vessels categorized per lymphosome as type 1 (medial), type 2 (other locations), or type 3 (absent); ISL staging and Maegawa lymphoscintigraphic staging used for severity correlation
Shinaoka et al[28]	2022	Japan	105 (84 lymphedema and 21 control)	Secondary	ICG fluorescence lymphography (Shinaoka)	Single assessment	ISL staging; multivariable logistic regression	Modified model AUC 0.834 vs clinical model AUC 0.792 ($P = .029$); PM defect OR 4.68; PL defect OR 3.50; double defect more severe than single ($P = .025$)	LPad classification: no defect (mildest), single PM or PL defect, double PM + PL defect, all groups defective (most severe); four lymphatic groups assessed: AM, AL, PM, PL

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Table I. Continued.

Study	Year	Country	N	Lymphedema type	Modality	Follow-up duration	Reference diagnostic standard	Main diagnostic values	Classification criteria
Treatment response assessment studies									
Keeley et al[29]	2023	UK	21	Primary and secondary	Perometry, BIS, TDC, ultrasound imaging (5-16 MHz), tonometry	5 days (groups B, C); 12 days (group A)	ISL staging (stage 2); limb volume by perometry as primary measure	Group A: LV reduction 109 mL ($P = .003$) day 1, 97 mL ($P = .024$) day 5; possible ECF decrease by BIS day 5; no consistent changes groups B/C; perometry CV 17.8%, BIS CV 21.1% most consistent measures	ISL stage 2 pitting edema; compression garment ≥20 mm Hg; exclusion: BMI >40, active cancer, venous insufficiency (reflux >2 s on duplex), heart/renal failure
Surgical planning studies									
Hara and Mihara[30]	2022	Japan	17 (32 limbs)	Secondary	Lymphatic ultrasound imaging	Single preoperative assessment	Intraoperative lymphatic diameter measurement; NECST classification; ISL staging; Maegawa lymphoscintigraphic classification	CSH-LD correlation $r = 0.36$ ($P = .003$); CSW-LD correlation $r = 0.24$ ($P = .050$); CSH/LD ratio 0.9 vs CSW/LD ratio 1.9; CSH differentiated ectasis from contraction type ($P = .0025$; AUC 0.78); CSW AUC 0.52	NECST classification: normal, ectasis, contraction, sclerosis types; D-CUPS criteria for lymphatic vessel identification on ultrasound; ISL stages 1-3; Maegawa types 1-5
Hayashi et al[31]	2016	Japan	26	Nonlymphedematous	Ultrasound imaging (Noblus, Hitachi; 15 MHz linear probe with color Doppler)	Single assessment	ICG lymphography	Sensitivity 95.5%; specificity 92.9%; lymphatic vessels detected in all 12 part 1 cases; average 1.6 ± 0.5 lymphatic vessels per leg in both modalities	Lymphatic vessels identified as homogeneous, hypoechoic, spicular misshapen images below superficial fascia; no color Doppler flow; distinguished from veins and nerves
Mihara et al[32]	2014	Japan	95	Primary and secondary	ICG lymphography	Mean 27.3 months (range, 12-57 months)	ISL staging; ICG lymphography findings; limb girth measurements	Mean cellulitis episodes reduced from 1.46 to 0.18 per year ($P < .001$); significant reduction in lower limb ($P < .001$), ISL stage 2a ($P = .007$), 2b ($P = .016$), stage 3 ($P = .020$); secondary lymphedema ($P < .001$)	ISL stages 0-3; lymphatic vessels and cutaneous veins 0.3-1 mm identified by ICG lymphography; cellulitis defined as fever ≥38.5 °C with warmth/redness in affected limb; minimum 3 anastomoses per limb

Table I. Continued.

Study	Year	Country	N	Lymphedema type	Modality	Follow-up duration	Reference diagnostic standard	Main diagnostic values	Classification criteria
Mixed upper and lower extremity studies									
Anatomical assessment and classification studies									
Hayashi et al[53]	2019	Belgium/ Japan	30 (13 UE and 17 LE)	Secondary	UHFUS imaging (70 MHz), CHFUS imaging (18 MHz)	Cross-sectional (single time point)	ICG lymphography (linear pattern confirmation of detected lymphatic vessels)	UHFUS imaging: sensitivity 94.9%, specificity 98.3%; CHFUS imaging: sensitivity 66.3%, specificity 91.3%; UHFUS imaging detected significantly more lymphatic vessels than CHFUS imaging in upper extremities (7.00 vs 4.15, $P < .001$) and lower extremities (4.59 vs 3.82, $P = .042$); UHFUS imaging detected smaller diameter vessels in upper extremities (0.336 vs 0.403 mm, $P < .001$) and lower extremities (0.417 vs 0.468 mm, $P < .001$)	Lymphatic vessel identification criteria: intermittent homogeneous, hypoechoic, and specular misshapen images in sagittal B-mode; no color on Doppler mode; no convergence with artery, vein, or nerve; UHFUS demonstrated novel findings including vessel resistance to collapse under transducer pressure and visualization of lymphatic fluid movement with functioning valves; vessels as small as 0.18 mm detected

AL, Anterolateral; *AM*, anteromedial; *AUC*, area under the curve; *BCRL*, breast cancer-related lymphedema; *BIS*, bioimpedance spectroscopy; *BMI*, body mass index; *CDP*, complex decongestive physiotherapy; *CDT*, complete decongestive therapy; *CHFUS*, conventional high-frequency ultrasound; *CI*, confidence interval; *CNR*, contrast-to-noise ratio; *CPT*, current procedural terminology; *CSH*, cross-sectional height; *CSW*, cross-sectional width; *CV*, coefficient of variation; *DE*, dependent edema; *D-CUPS*, diagnostic criteria for ultrasound identification of lymphatic vessels; *ECF*, extracellular fluid; *HBO*, hyperbaric oxygen; *HFUS*, high-frequency ultrasound; *ICC*, intraclass correlation coefficient; *ICG*, indocyanine green; *IPC*, intermittent pneumatic compression; *IQR*, interquartile range; *ISL*, International Society of Lymphology; *κ*, kappa coefficient; *LAS*, lymphatic activity score; *LD*, lymphatic diameter; *L-Dex*, lymphedema index; *LE*, lower extremity; *LG-MLD*, lymphoscintigraphically guided manual lymphatic drainage; *LLIS*, Lymphedema Life Impact Scale; *LPad*, lymphatic pathway defects; *LSG*, lymphoscintigraphy; *LV*, limb volume; *LVA*, lymphaticovenular anastomosis; *MFBIA*, multifrequency bioelectrical impedance analysis; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *MRL*, magnetic resonance lymphangiography; *NECST*, normal ectasis contraction sclerosis type; *NIRF-L*, near infrared fluorescence lymphangiography; *OR*, odds ratio; *PL*, posterolateral; *PM*, posteromedial; *PPV*, positive predictive value; *PROM*, patient reported outcome measure; *PSM*, prospective surveillance model; *RCT*, randomized controlled trial; *RR*, relative risk; *SCaT*, saphenous calf thigh; *Se*, sensitivity; *SEF*, echo free space grade; *SEG*, subcutaneous echogenicity grade; *SNR*, signal-to-noise ratio; *Sp*, specificity; *SPECT/CT*, single photon emission computed tomography/computed tomography; *St-MLD*, standardized manual lymphatic drainage; *SWV*, shear wave velocity; *TDC*, tissue dielectric constant; *TM*, tape measurement; *T2WI*, XXX; *99mTc*, technetium 99m; *UE*, upper extremity; *UHFUS*, ultra-high-frequency ultrasound; *ULL 27*, Upper Limb Lymphedema 27 questionnaire; *VLNT*, vascularized lymph node transfer.
BIS is classified as a "Diagnostic and Surveillance Tool" rather than an imaging modality because it measures tissue fluid accumulation through bioelectrical impedance rather than producing anatomical images. "Cross-sectional (single time point)" indicates that the study assessed diagnostic performance at a single evaluation without longitudinal follow-up. Studies with longitudinal follow-up report the specific duration. Where specific sensitivity and specificity values were not reported in the original study, the main diagnostic contribution is described qualitatively.

Data synthesis methods. Quantitative meta-analysis was not performed because of substantial differences across the included studies. Specifically, the studies used a wide variety of diagnostic tests (eg, BIS, ICG lymphography, MRL, LSG, and US imaging), each with different technical parameters. The reference standards used to confirm lymphedema diagnosis also varied considerably. Some studies used clinical examination and limb volume measurements; others used LSG and circumferential tape measurements with different threshold criteria. Furthermore, the definitions of what constituted a "positive" diagnosis differed across studies (eg, volume increase ≥10% vs ≥200 mL vs L-Dex threshold >6.5). These combined differences made it inappropriate to pool results statistically. Therefore, a qualitative narrative synthesis was conducted, organized by anatomical region (upper extremity vs lower extremity) and imaging and diagnostic modalities.

RESULTS

Study selection

The database search yielded 2847 total records. After removal of 936 duplicates, 1911 unique records were screened by title and abstract, of which 1867 were excluded as irrelevant. Forty-four full-text articles were assessed for eligibility. A total of 23 primary studies were included. In addition, five systematic reviews and meta-analyses were included to provide broader context and to supplement the findings of the primary studies by summarizing evidence from larger bodies of literature on specific imaging modalities. The PRISMA 2020 flow diagram is presented in the Fig.

Study characteristics

Table I summarizes key characteristics of all included primary studies. Studies originated from Europe, Asia, North America, South America, and Australia among

primary studies, with systematic reviews drawing from international literature. Sample sizes in primary studies ranged from 6 to 141 participants for diagnostic accuracy evaluations and up to 1191 participants for RCTs. There were four RCTs (Ridner et al,[16] Gothard et al,[19] Bok et al,[20] and Barbieux et al[21]), 12 prospective diagnostic studies (Notohamiprodjo et al,[26] Hayashi et al,[31] Hayashi et al,[33] Weiss et al,[22] Fu et al,[11] Ward et al,[12] Mihara et al,[14] Bae et al,[15] Cornish et al,[13] Lu et al,[23] Mihara et al,[32] and Lohrmann et al[24]), three prospective cohort studies (Stout et al,[17] Hara and Mihara,[30] and Keeley et al[29]), three retrospective cohort studies (Wiser et al,[18] Hara and Mihara,[27] and Shinaoka et al[28]), and one observational study (Suehiro et al[25]).

Upper extremity results

Diagnostic accuracy studies. Fu et al[11] conducted a prospective diagnostic accuracy study of 141 women with BCRL, evaluating the L-Dex ratio for detecting and diagnosing lymphedema. BIS works by sending a painless, low-level electrical current through the limbs to measure the amount of fluid in the tissue outside of cells (extracellular fluid [ECF]).[30] The L-Dex score is a numerical value derived from BIS that reflects this fluid level. Each patient's L-Dex score is measured before cancer treatment to establish a personal baseline. An increase in the L-Dex score of more than 6.5 units above that individual's baseline indicates a clinically meaningful increase in arm fluid, suggesting early (subclinical) lymphedema before visible swelling occurs.[29,30] Fu et al[11] demonstrated a BIS sensitivity of 80% (95% CI, 0.66-0.89) and a specificity of 90% (95% CI, 0.84-0.94), with an L-Dex score greater than 7.1 serving as the diagnostic criterion. This study established the primary diagnostic thresholds used in subsequent surveillance trials.

Ward et al[12] conducted a diagnostic study of 15 postmastectomy patients and 15 controls evaluating multifrequency bioelectrical impedance analysis (MFBIA) for lymphedema diagnosis and monitoring. The technique demonstrated quantitative agreement with clinical diagnosis of lymphedema and with limb volume calculated from circumferential measurements, confirming that observed changes in limb volume were attributable to accumulation of ECF. The authors concluded that MFBIA potentially offers the means for earlier definitive diagnosis and more accurate monitoring of ECF changes during and after treatment, establishing foundational evidence for BIS technology in lymphedema assessment.

Cornish et al[13] conducted a 3-year prospective study of 102 patients undergoing surgery for breast cancer and 60 healthy control subjects, evaluating MFBIA for early detection of lymphedema. Twenty patients developed lymphedema during the 24-month follow-up period, and MFBIA predicted the onset of lymphedema in each case up to 10 months before the condition could be clinically diagnosed. The technique demonstrated a sensitivity of 100% and a specificity of 98%, compared with a sensitivity of only 5% for circumferential limb volume measurements for the purpose of early detection. At the time of detection by MFBIA, only one of the 20 patients who developed lymphedema returned a positive test result from limb volumes determined by circumferential measurements. These findings confirmed the suitability of the MFBIA technique as a reliable and noninvasive diagnostic procedure for the early detection of lymphedema, contributing to the foundational evidence supporting BIS technology in clinical practice.

Mihara et al[14] conducted a prospective comparative diagnostic study of 32 patients evaluating ICG lymphography vs LSG for early upper limb lymphedema. ICG demonstrated 100% diagnostic accuracy compared with 62% sensitivity for LSG, establishing NIRF-L superiority over LSG for early-stage upper extremity disease. This study provided foundational evidence for the adoption of ICG lymphography in clinical practice.

Bae et al[15] conducted a prospective comparative diagnostic study of 22 patients evaluating MRL vs LSG for upper extremity lymphedema. MRL demonstrated a sensitivity of 92% to 100% and a specificity of 85% to 100% for detection of abnormal lymphatic vessels. This study supported the complementary value of MRL and LSG for comprehensive upper extremity assessment.

Anatomical assessment and classification studies. Hayashi et al[33] conducted a comparative diagnostic study of 30 patients with unilateral secondary lymphedema (13 upper limbs and 17 lower limbs), evaluating ultra-high-frequency US (UHFUS) imaging at 70 MHz compared with conventional high-frequency US (CHFUS) imaging at 18 MHz for detection of lymphatic vessels. UHFUS imaging detected 169 lymphatic vessels compared with 118 detected by CHFUS imaging, with significantly more vessels identified in both upper extremities (7.00 vs 4.15; $P < .001$) and lower extremities (4.59 vs 3.82; $P = .042$). UHFUS imaging demonstrated a sensitivity of 94.9% and a specificity of 98.3% for lymphatic vessel detection compared with 66.3% sensitivity and 91.3% specificity for CHFUS imaging, using ICG lymphography as the reference standard. UHFUS imaging detected lymphatic vessels with significantly smaller diameters than CHFUS imaging in both upper extremities (0.336 vs 0.403 mm; $P < .001$) and lower extremities (0.417 vs 0.468 mm; $P < .001$), including vessels smaller than 0.3 mm. In addition, UHFUS imaging revealed novel characteristics including lymphatic vessel resistance to collapse under transducer pressure and visualization of lymphatic fluid movement with functioning valves, features not observable with CHFUS imaging.

Surveillance and early detection studies. Ridner et al[16] conducted the landmark PREVENT trial, a multicenter RCT of 879 patients with breast cancer who were

Table II. Technical parameters for imaging and diagnostic modalities in lymphedema assessment

Parameter	Bioimpedance spectroscopy (BIS)	Near-infrared fluorescence lymphangiography (NIRF-L/ICG)	Magnetic resonance lymphangiography (MRL)	High-frequency ultrasound (HFUS) imaging	Lymphoscintigraphy (LSG)	Computed tomography (CT) and SPECT/CT
Modality category	Diagnostic/ surveillance Tool	Imaging modality	Imaging modality	Imaging modality	Imaging modality	Imaging modality
Device/ equipment	L-Dex U400 (ImpediMed); FDA-cleared in 2008	Near-infrared fluorescence camera operating at excitation of 760-785 nm and emission of 820-840 nm; commonly PDE (Hamamatsu), IC-View (Pulsion), or SPY (Stryker/ Novadaq)	1.5-T or 3.0-T MRI scanner; 3.0 T preferred for higher spatial resolution and signal-to-noise ratio	Linear-array high-frequency transducer; 20-70 MHz; 70-MHz scanner (eg, Vevo MD, FUJIFILM VisualSonics) for ultrahigh resolution	Large field-of-view gamma camera with low-energy, high-resolution (LEHR) collimator	Standard CT scanner; SPECT/CT combines gamma camera with CT
Contrast/tracer agent	None (measures bioelectrical impedance)	Indocyanine green (ICG); 0.25% concentration (2.5 mg/mL); reconstituted with sterile water or normal saline	Gadolinium-based contrast agent (GBCA); commonly gadobutrol (Gadovist) or gadopentetate dimeglumine (Magnevist); diluted 1:10 to 1:20	None (B-mode ultrasound imaging)	Technetium-99m (^{99}Tc)-labeled colloid; commonly ^{99m}Tc-sulfur colloid (USA), ^{99m}Tc-nanocolloid (Europe), or ^{99m}Tc-antimony trisulfide colloid (Australia); particle size 5-100 nm	Standard CT: IV iodinated contrast (if used); SPECT/CT: ^{99}Tc-labeled colloid (same as LSG)
Dose	Not applicable	0.1-0.3 mL per injection site (0.025-0.075 mg ICG per site)	0.2-0.5 mL of diluted GBCA per injection site	Not applicable	0.2-0.5 mCi (7.4-18.5 MBq) per injection site; total 0.5-1.5 mCi (18.5-55.5 MBq) per limb	Standard CT: per institutional protocol; SPECT/CT: same as LSG
Administration route	Tetrapolar electrode configuration on skin surface	Intradermal injection	Intradermal injection	Transcutaneous (probe placed on skin surface with coupling gel)	Intradermal or subcutaneous injection	IV (CT contrast); intradermal or subcutaneous (SPECT/CT radiotracer)
Injection/ electrode sites: UE	Two drive electrodes on ipsilateral hand (dorsum) and foot (dorsum); two sense electrodes on ipsilateral wrist and ankle; contralateral limb measured simultaneously	Dorsal web spaces of the hand (2nd, 3rd, and 4th web spaces) and/or volar wrist; 3-4 injection sites per limb	Dorsal web spaces of the hand (2nd and 3rd web spaces); 2-4 sites per limb	Not applicable (probe placed along expected lymphatic vessel course on medial upper arm and forearm)	Dorsal web spaces of the hand (2nd and 3rd web spaces); 2-4 sites per limb	Not applicable (IV contrast for CT)
Injection/ electrode sites: LE	Same electrode configuration as UE (hand, foot, wrist, and ankle)	Dorsal web spaces of the foot (1st, 2nd, and 3rd web spaces), medial ankle, and/or dorsum of foot; 4-6 injection sites per limb	Dorsal web spaces of the foot (1st, 2nd, and 3rd web spaces) and/or medial ankle; 4-6 sites per limb	Not applicable (probe placed along medial lower leg, popliteal fossa, medial thigh, and inguinal region)	Dorsal web spaces of the foot (1st, 2nd, and 3rd web spaces); 2-4 sites per limb	Not applicable

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Table II. Continued.

Parameter	Bioimpedance spectroscopy (BIS)	Near-infrared fluorescence lymphangiography (NIRF-L/ICG)	Magnetic resonance lymphangiography (MRL)	High-frequency ultrasound (HFUS) imaging	Lymphoscintigraphy (LSG)	Computed tomography (CT) and SPECT/CT
Measurement frequency/ sequences	Multifrequency bioelectrical impedance; 256 frequencies between 3 kHz and 1000 kHz	Single-wavelength near-infrared fluorescence (excitation 760-785 nm, emission 820-840 nm)	Three-dimensional T1-weighted gradient echo with fat suppression (VIBE, THRIVE, or LAVA); pre- and serial postcontrast acquisitions; T2-weighted sequences (STIR or HASTE) for edema assessment	20-70 MHz B-mode ultrasound imaging; 70 MHz for highest-resolution superficial vessel imaging; 20-50 MHz for deeper structures	Dynamic gamma camera acquisition; static anterior and posterior views	Standard CT protocols; SPECT/CT adds three-dimensional radiotracer localization
Imaging depth	Not applicable (measures whole-limb extracellular fluid ratio)	Superficial lymphatic system only; maximum penetration <2 cm from skin surface	Superficial and deep lymphatic collectors; full cross-sectional visualization including subfascial and epifascial compartments	Approximately 5-10 mm at 70 MHz; 10-20 mm at 20-30 MHz	Whole-limb functional assessment including superficial and deep systems; limited spatial resolution for individual vessels	Full cross-sectional anatomical visualization
Patient positioning	Supine with limbs abducted approximately 30° from body; skin cleaned with alcohol; jewelry removed; minimum 10-minute rest period	Supine for UE; supine and prone (or lateral decubitus) for LE to visualize anterior and posterior drainage pathways; darkened examination room required	Supine on MRI table; limbs positioned symmetrically; may require multiple station acquisitions with table repositioning	Supine or seated with limb supported; coupling gel applied; skin clean and dry	Supine on imaging table; limbs positioned symmetrically for bilateral comparison	Supine on CT/ SPECT table
Imaging/ acquisition timing	Single measurement at each visit (approximately 3-5 minutes per bilateral assessment)	Initial imaging 5-15 minutes postinjection (linear pathway visualization); 30-60 minutes (dermal backflow assessment); 60-120 minutes for complete LE assessment	Precontrast baseline; serial postcontrast at 5, 10, 15, 20, 30, 45, and 60 minutes; LE may require delayed acquisitions at 75-90 minutes	Real-time continuous scanning during examination	Dynamic: continuous for first 30-60 minutes; Static: at 30 minutes, 1 hour, 2 hours, and 3-4 hours; LE delayed images at 4-6 hours	Standard CT: single acquisition; SPECT/CT: acquired with LSG protocol
Examination duration: UE	Approximately 3-5 minutes	Approximately 30-45 minutes	Approximately 50 minutes	Approximately 20-30 minutes	Approximately 2-3 hours (including delayed images)	CT: 5-10 minutes; SPECT/CT: added to LSG protocol
Examination duration: LE	Approximately 3-5 minutes	Approximately 60-90 minutes	Approximately 75-90 minutes	Approximately 30-60 minutes	Approximately 3-6 hours (including delayed images)	CT: 5-10 minutes; SPECT/CT: added to LSG protocol

Table II. Continued.

Parameter	Bioimpedance spectroscopy (BIS)	Near-infrared fluorescence lymphangiography (NIRF-L/ICG)	Magnetic resonance lymphangiography (MRL)	High-frequency ultrasound (HFUS) imaging	Lymphoscintigraphy (LSG)	Computed tomography (CT) and SPECT/CT
Measurement output	L-Dex score: unitless ratio derived from impedance ratio between affected and unaffected limbs at zero frequency (R_0), reflecting extracellular fluid differences	Real-time fluorescence video and static images showing lymphatic vessel course, flow direction, and dermal backflow patterns	Three-dimensional T1-weighted images showing lymphatic vessel morphology, lymph node enhancement, and tissue edema; subtraction images and MIP reconstructions	B-mode images showing lymphatic vessel diameter, wall thickness, lumen patency, and vessel morphology	Planar scintigraphic images showing lymphatic channel visualization, lymph node uptake, dermal backflow, and transport kinetics	CT: cross-sectional anatomical images; SPECT/CT: 3D functional-anatomical fusion images
Diagnostic thresholds/ classification	L-Dex >7.1: diagnostic criterion without baseline; L-Dex change >6.5 from preoperative baseline: surveillance trigger for early conservative intervention	UE: Yamamoto classification (linear, splash, stardust, diffuse); LE: SCaT classification (saphenous, calf, thigh; 0-3 per region, total 0-9) and Shinaoka classification (pathway defects correlating with ISL stage)	Abnormal lymphatic vessel morphology and asymmetric enhancement; dilated collectors; dermal backflow; honeycomb subcutaneous tissue pattern; epifascial fluid	Vessel diameter ≥0.3 mm; sclerosis classification types 1-4 (Mihara et al): type 1 normal wall/ patent lumen, type 2 mildly thickened/ patent, type 3 significantly thickened/ narrowed, type 4 obliterated; types 1-2 suitable for LVA	Transport index (Kleinhans): normal <10; clearance half-time; nodal uptake asymmetry ratio; qualitative assessment of channel visualization, nodal uptake, and dermal backflow	CT sensitivity 33%-62%, specificity >95%; primarily for differential diagnosis
Sensitivity	80% (95% CI, 0.66-0.89) (Fu et al[11])	UE: 97%-100%; LE: 97%-100%	92%-100% (both UE and LE)	86% for vessel detection vs NIRF-L	62% for early UE lymphedema; higher for advanced disease	33%-62%
Specificity	90% (95% CI, 0.84-0.94) (Fu et al[11])	Not formally reported across included studies	85%-100% (UE; Bae et al[15])	Not formally reported	Not formally reported across included studies	>95%
Reliability	ICC, 0.95-0.99 inter- and intrarater (Ward et al[12])	Not formally reported	Not formally reported	Not formally reported	Not formally reported	Not applicable
Surveillance protocol	Preoperative baseline, then every 3-6 months postoperatively for minimum 24-36 months; every 3 months in first 12 months post-ALND	Not applicable (used for diagnostic and surgical planning, not longitudinal surveillance)	Not applicable (used for diagnostic and surgical planning)	Not applicable (used for preoperative mapping)	Not applicable (used for baseline functional assessment)	Not applicable
Early intervention trigger	L-Dex change >6.5 from baseline: class 2 compression sleeve and gauntlet for 4 weeks with follow-up BIS	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

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Table II. Continued.

Parameter	Bioimpedance spectroscopy (BIS)	Near-infrared fluorescence lymphangiography (NIRF-L/ICG)	Magnetic resonance lymphangiography (MRL)	High-frequency ultrasound (HFUS) imaging	Lymphoscintigraphy (LSG)	Computed tomography (CT) and SPECT/CT
Contraindications	Bilateral lymphedema (requires unaffected contralateral limb); patients with pacemakers or implanted electronic devices	Iodine allergy (ICG contains sodium iodide); severe hepatic insufficiency; caution in pregnancy	Pacemakers and certain metallic implants; severe renal insufficiency (nephrogenic systemic fibrosis risk with GBCA); claustrophobia; pregnancy (relative); gadolinium allergy	None reported	Pregnancy and breastfeeding (radiation exposure); allergy to colloid components	Pregnancy (radiation); iodinated contrast allergy (CT); renal insufficiency (CT contrast)
Limitations	Requires unaffected contralateral limb; does not capture fibrotic changes; no anatomical detail; affected by hydration, temperature, and exercise; no validated LE thresholds	Depth <2 cm; cannot visualize deep collectors or pelvic/retroperitoneal nodes; requires darkened room; operator-dependent; LE requires longer time and more injection sites	High cost; limited availability; long examination time (especially LE); requires trained radiologist; GBCA contraindicated in renal impairment; motion artifact; not suitable for intraoperative use	Highly operator-dependent; specialized probes with limited availability; limited depth; no standardized protocol; steep learning curve; time-consuming for LE; limited field of view	Variable sensitivity (especially early disease); low spatial resolution; radiation exposure; invasive injection; requires nuclear medicine department; extended imaging time (especially LE); semiquantitative	Poor lymphatic vessel visualization; radiation exposure; high cost; limited to differential diagnosis; not recommended as a primary lymphedema diagnostic tool
Source studies	Fu et al,[11] Ridner et al,[16] Ward et al,[12] Cornish et al,[13] Stout et al,[17] Keeley et al[29]	Mihara et al,[32] Wiser et al,[18] Hara and Mihara,[27] Shinaoka et al,[28] Hayashi et al[33]	Notohamiprodjo et al,[26] Bae et al,[15] Lu et al,[23] Lohrmann et al,[24] Weiss et al,[22] Miseré et al,[37] Quartuccio et al[36]	Hayashi et al,[31] Hayashi et al,[33] Mihara et al[14]	Mihara et al,[14] Gothard et al,[19] Weiss et al,[22] Barbieux et al,[21] Notohamiprodjo et al[26]	van Heumen et al,[7] Weiss et al[22]

ALND, Axillary lymph node dissection; *CI*, confidence interval; *DVT*, deep vein thrombosis; FDA, Food and Drug Administration; *ICC*, intraclass correlation coefficient; *ISL*, International Society of Lymphology; *IV*, intravenous; *L-Dex*, lymphedema index; *LE*, lower extremity; *LVA*, lymphovenous anastomosis; *MIP*, maximum intensity projection; *MRI*, magnetic resonance imaging; *RCT*, randomized controlled trial; *SPECT*, single-photon emission computed tomography; *UE*, upper extremity.
BIS is classified as a "Diagnostic and Surveillance Tool" rather than an imaging modality because it measures tissue fluid accumulation through bioelectrical impedance rather than producing anatomical images. All other modalities are classified as "Imaging Modalities." Technical parameters represent the range of protocols reported across included studies rather than a single standardized protocol. Clinicians should adapt protocols based on available equipment, institutional expertise, and individual patient factors. Where specific sensitivity, specificity, or reliability values were not formally reported in the original studies, this is indicated as "Not formally reported".

analyzed (963 randomized) comparing BIS surveillance with tape measurement surveillance over a median follow-up of 32.9 months. Patients who received BIS surveillance triggered intervention at a lower rate (20.1% vs 27.5%; $P = .011$) with longer median times to trigger intervention (9.7 vs 3.9 months; $P = .001$). Among 209 triggered patients, BIS significantly reduced progression to chronic lymphedema requiring complex decongestive physiotherapy compared with tape measurement (7.9% vs 19.2%; relative risk = 0.41; absolute reduction, 11.3%; $P = .016$). This means that for every 100 patients monitored, approximately 11 fewer patients developed chronic lymphedema when BIS-triggered surveillance was used (11.3% absolute risk reduction).

Stout et al[17] conducted a cost analysis comparing direct treatment costs of a prospective surveillance model with a traditional model of care for BCRL using the 2009 Medicare physician fee schedule. The prospective surveillance model cost $636.19 per patient per year compared with $3124.92 for the traditional model, and $38,272.83 vs $104,684.82 per 100 patients. Sensitivity analysis demonstrated that 80.5% of early-stage patients would have to progress to advanced-stage lymphedema before the prospective surveillance model cost would exceed the traditional model, providing economic justification for prospective surveillance with early conservative intervention.

Surgical planning studies. Wiser et al[18] conducted a prospective cohort study of 118 patients with unilateral upper extremity secondary lymphedema evaluating the most commonly used preoperative assessment tools for surgical candidates. The preoperative assessment included limb volume measurements, BIS, ICG lymphography, LSG, magnetic resonance angiography

(MRA), and patient-reported outcome questionnaires. ICG lymphography demonstrated the highest sensitivity for detecting lymphedema, with 100% of affected limbs exhibiting pathological dermal backflow patterns classified by the Yamamoto staging system, including splash (20.6%), stardust (63.9%), and diffuse (15.5%) patterns. L-Dex bioimpedance scores were highly correlated with limb volume excess ($r^2 = 0.714$; $P < .001$) and demonstrated a sensitivity of 91.2% and a positive predictive value of 87.3% for diagnosing lymphedema defined as a limb volume difference greater than 10%. LSG demonstrated a sensitivity of 88% but a low specificity of 41.4%, while MRA was highly sensitive for detecting fluid accumulation (94.2%) and fat hypertrophy (96.2%) and identified axillary venous stenosis in 15.4% of patients. The authors concluded that preoperative assessment of lymphedema requires a multimodal approach, as no single metric adequately represents the state of disease, and that MRA, L-Dex, ICG, and patient-reported outcome measures are all valuable components of comprehensive surgical evaluation.

Treatment response assessment studies. Three RCTs used imaging and diagnostic modalities as outcome assessment tools to evaluate therapeutic interventions for upper extremity lymphedema. Gothard et al[19] conducted a randomized phase II trial of 58 patients with chronic arm lymphedema (≥15% volume increase) after radiotherapy for cancer, randomized 2:1 to hyperbaric oxygen therapy (n = 38) or best standard care (n = 20). Multiple imaging and diagnostic modalities were used as outcome assessment tools, including perometry for limb volume measurement as the primary end point, LSG to quantify lymphatic clearance rates of 99mTc-nanocolloid tracer, and dielectric constant measurements to assess extracellular water content. At 12 months, no statistically significant differences were found between groups in any of these diagnostic measures ($P = .93$ for volume change).

Bok et al[20] conducted a prospective RCT of 45 patients with stage II postmastectomy lymphedema, randomized to three groups based on intermittent pneumatic compression pressure: 25, 35, and 45 mm Hg. Acoustic radiation force impulse (ARFI) imaging, an US-based elastography modality, was used to quantitatively assess tissue stiffness by measuring shear wave velocity (SWV) in subcutaneous tissue. Arm circumference and subcutaneous tissue thickness decreased significantly after a single 30-minute intermittent pneumatic compression session in all groups. However, SWV decreased significantly only in the 35 mm Hg group (mean reduction 0.40 m/s; $P = .02$). A positive correlation was found between reduction in SWV and subcutaneous tissue thickness ($r = 0.63$; $P = .00$), demonstrating ARFI's utility as a noninvasive imaging tool for objectively quantifying tissue stiffness changes in response to compression therapy.

Barbieux et al[21] conducted a randomized clinical trial of 52 patients with secondary upper limb lymphedema, comparing lymphoscintigraphically guided manual lymphatic drainage with standardized manual lymphatic drainage (St-MLD). LSG, using 99mTc-nanocolloid tracer injected subcutaneously, served as both diagnostic imaging modality and therapeutic guidance tool, quantifying radioactive activity in regions of interest including axillary lymph nodes and areas of dermal backflow. Results demonstrated that a single session of St-MLD increased lymph node activity by 28% on average and decreased dermal backflow activity by 11%. Notably, lymphoscintigraphically guided manual lymphatic drainage was 19% more efficient than St-MLD in increasing lymph node activity during the second phase of treatment ($P = .0210$), while both techniques decreased dermal backflow activity with equal intensity. These findings demonstrate that LSG can serve not only as a diagnostic imaging tool but also as a therapeutic guidance modality, enabling physical therapists to adapt manual lymphatic drainage to the patient's individual lymphatic anatomy and physiology for improved treatment outcomes.

Systematic reviews and meta-analyses. Shah et al[34] conducted a meta-analysis of 50 studies including more than 67,000 women evaluating the impact of BIS vs circumference measurements on the incidence of chronic BCRL. BIS monitoring with early intervention significantly reduced the relative risk of chronic BCRL by 69% compared with background monitoring and 81% compared with circumference monitoring. Circumference monitoring did not provide a benefit compared with background rates. The pooled annualized incidence rate in BIS-monitored cohorts was 1.5%, compared with 7.7% for circumference monitoring and 4.9% for background.

Rafn et al[35] conducted a systematic review and meta-analysis of 23 studies encompassing 5584 participants that assessed whether prospective surveillance and early management reduced the risk of chronic BCRL. Early detection and management reduced the rate of chronic BCRL by 50%. However, eight different measurement methods and 25 different diagnostic criteria were used across studies. The authors concluded that surveillance should be offered to patients undergoing axillary lymph node dissection up to 24 months postoperatively.

Quartuccio et al[36] conducted a systematic review of 11 studies comparing LSG and MRI techniques. The sensitivity of MRI techniques, especially MRL, appeared superior to LSG for diagnosing upper limb lymphedema. MRL and LSG provide complementary findings, and combined use was recommended for comprehensive assessment.

Van Heumen et al[7] conducted a systematic review of 129 studies analyzing imaging modalities for lymphatic vessel visualization in surgical planning, identifying six

imaging modalities. NIRF-L was the most frequently studied modality. The authors concluded that combined use of NIRF-L for superficial assessment and MRL for deep assessment provides complementary information and may improve lymphovenous anastomosis (LVA) and vascularized lymph node transfer success.

Lower extremity results

Diagnostic accuracy studies. Weiss et al[22] conducted a prospective study of 34 patients (28 female; age range, 27-83 years) with suspected primary lower limb lymphedema, comparing planar LSG (67 lower limbs) with SPECT/CT (65 anatomic sites) using 99mTc-nanocolloid. Planar LSG identified lymphatic disorders in 28 limbs, and SPECT/CT provided additional diagnostic information in 96.4% of pathological cases, including improved anatomical allocation of lymphatic disorders (64%), enhanced three-dimensional detection of dermal backflow (86%), and verification of lymph node presence or absence (46%).

Lu et al[23] conducted a comparative diagnostic imaging study of 40 lower extremities in 31 patients with primary lymphedema, evaluating noncontrast heavily T2-weighted MRI and interstitial MRL with intracutaneous injection of gadobenate dimeglumine. Lymphangiectatic lesions were detected on heavily T2-weighted MRI in 97.5% of lower extremities at the lower leg level compared with 90% on MRL. Heavily T2-weighted imaging visualized significantly more dilated lymphatic vessels (mean, 6.82 vs 4.88; $P = .003$) with larger maximum diameters (4.28 vs 3.41 mm; $P < .01$) and identified greater regions of accumulated lymph fluid and honeycombing pattern involvement (both $P < .01$). However, MRL demonstrated a significantly higher signal-to-noise ratio, contrast-to-noise ratio, and superior image quality scores (all $P < .01$). The authors concluded that heavily T2-weighted imaging provided greater sensitivity for detecting modified lymphatic vessels, and MRL offered higher image legibility.

Lohrmann et al[24] conducted a prospective study of 13 patients (26 lower extremities; five lipedema, eight lipo-lymphedema) evaluating MRL using intracutaneous gadoteridol injection on a 1.5-T system. All 16 lipo-lymphedema extremities demonstrated epifascial lymphedema on imaging, while none of the 10 pure lipedema extremities showed lymphedema. However, MRL detected enlarged lymphatic vessels up to 2 mm in six extremities of clinically pure lipedema patients, indicating subclinical lymphatic impairment not identified by clinical examination. The study demonstrated MRL as a safe, minimally invasive modality capable of differentiating lipedema from lipo-lymphedema to optimize therapeutic planning.

Suehiro et al[25] conducted a retrospective study comparing subcutaneous US findings between dependent edema (20 legs, 10 patients) and secondary lymphedema (54 legs, 35 patients) using an 8 to 12 MHz linear transducer. Subcutaneous echogenicity grade and echo-free space grade were assessed at eight standardized points. In dependent edema, increased echogenicity followed gravity distribution, while in lymphedema, echogenicity correlated with the ventromedial lymphatic bundle and ISL clinical stage. The study demonstrated that US imaging can differentiate dependent edema from lymphedema based on distinct subcutaneous tissue change patterns.

Notohamiprodjo et al[26] prospectively compared MRL at 3.0 T with LSG in 30 patients (57-60 extremities) with lower extremity lymphedema. Both modalities achieved 100% sensitivity/specificity for delayed drainage ($\kappa = 0.93$). MRL demonstrated superior sensitivity for lymph vessel abnormalities (100% vs 79%), detecting vessels masked by dermal backflow on LSG, while LSG showed higher specificity for lymph node depiction (100% vs 78%). The study established MRL as a complementary modality with advantages in lymph vessel visualization and presurgical planning.

Anatomical assessment and classification studies. Hara and Mihara[27] conducted a retrospective study of 105 patients (210 lower limbs; 630 lymphosomes) developing the saphenous calf thigh (SCaT) classification based on multilymphosome ICG lymphography. ICG was injected at three sites corresponding to the saphenous, lateral calf, and lateral thigh lymphosomes, with lymphatic vessels categorized as type 1 (medial), type 2 (other locations), or type 3 (absent). Results showed lymphatic vessels shifted from medial to lateral and eventually disappeared as lymphedema severity progressed. The SCaT classification provides a comprehensive multilymphosome staging system for guiding interdisciplinary lymphedema management.

Shinaoka et al[28] conducted a retrospective study of 84 patients with secondary lymphedema (164 lower limbs) and 21 control participants (42 lower limbs) developing the lymphatic pathway defects (LPad) severity classification based on ICG fluorescence lymphography. Using a novel five-site injection protocol, four independent lymphatic vessel groups (anteromedial, anterolateral, posteromedial, and posterolateral) were visualized. Multivariable logistic regression demonstrated that defects in the posteromedial and posterolateral groups were independently associated with lymphedema severity. The modified severity model incorporating these pathway defects (AUC, 0.834) was significantly superior to the clinical model alone (AUC, 0.792; $P = .029$). The LPad classification stages lymphedema from no defects (mildest) to single, double, and complete lymphatic group defects (most severe), providing a pathogenesis-based severity staging system that complements existing phenotype-based classifications.

Treatment response assessment studies. Keeley et al[29] conducted a prospective, randomized

preliminary study of 21 participants (86% female; 81% primary lymphedema; ISL stage 2) comparing three PCD dosing protocols for lower extremity lymphedema: (1) 1 hour daily for 12 days, (2) 1 hour twice daily for 5 days, or (3) 2 hours twice daily for 5 days. Group A demonstrated significant limb volume reductions of 109 mL ($P = .003$) on day 1 and 97 mL ($P = .024$) on day 5, with possible ECF decreases by BIS on day 5; groups B and C showed no consistent changes. Among all measurements assessed, perometry and BIS demonstrated the greatest consistency and responsiveness to change. On the other hand, tonometry, US imaging, and tissue dielectric constant provided lesser utility.

Surgical planning studies. Hara and Mihara[30] conducted a study of 17 patients (32 lower limbs; 68 lymphatic vessels) evaluating the accuracy of lymphatic US imaging using an 18 MHz linear probe (Noblus; Hitachi) for measuring lymphatic vessel size in lower extremity lymphedema. Preoperative US imaging measurements of cross-sectional height (CSH) and cross-sectional width (CSW) were compared with actual lymphatic diameter (LD) measured intraoperatively during LVA. CSH showed a stronger correlation with LD ($r = 0.36$; $P = .003$) than CSW ($r = 0.24$; $P = .050$), with a mean CSH/LD ratio of 0.9 vs a CSW/LD ratio of 1.9. CSH significantly differentiated ectasis from contraction types on the normal ectasis contraction sclerosis type classification ($P = .0025$; AUC, 0.78), while CSW did not (AUC, 0.52). The study demonstrated that CSH is a more reliable preoperative index for predicting lymphatic vessel size and selecting optimal ectasis-type vessels for LVA.

Hayashi et al[31] conducted a two-part study evaluating the visualization of lymphatic vessels in the lower leg using US imaging with a 15 MHz linear probe (Noblus; Hitachi) with color Doppler mode. In part 1, lymphatic vessels were identified by US imaging in 12 healthy volunteers with confirmed ICG lymphography linear patterns, establishing characteristic findings of homogeneous, hypoechoic, and spicular misshapen images located below the superficial fascia. In part 2, 14 additional healthy volunteers underwent US imaging-first lymphatic vessel identification followed by ICG lymphography confirmation, demonstrating 95.5% sensitivity and 92.9% specificity for lymphatic vessel detection. The study established that US imaging can reliably distinguish lymphatic vessels from blood vessels and nerves based on shape, echogenicity, location, and absence of color Doppler flow, and may complement ICG lymphography for preoperative LVA planning.

Mihara et al[32] conducted a retrospective study of 95 patients (84 lower limb, 11 upper limb) with lymphedema evaluating the effectiveness of LVA for reducing cellulitis. ICG lymphography was used as the primary diagnostic imaging modality for confirming lymphedema and identifying functional lymphatic vessels for surgical planning. The study demonstrated that LVA significantly reduced mean cellulitis episodes from 1.46 to 0.18 per year ($P < .001$). In addition, the study showed that an imaging-guided surgical approach enabled precise identification of lymphatic vessels and cutaneous veins of diameter 0.3 to 1 mm for anastomosis. Although the study's primary focus was on clinical outcomes of LVA, it established ICG lymphography as an effective tool for preoperative lymphatic mapping to guide surgical intervention in both upper and lower extremity lymphedema.

Systematic reviews. Miseré et al[37] conducted a systematic review of MRL in peripheral lymphedema encompassing 25 studies with 1609 patients in mixed upper and lower extremity presentations. MRL examination time was longer for the lower limb at 75 minutes compared with 50 minutes for the upper limb. A higher identification rate was noted in the lower leg compared with the upper leg. MRL visualizes afferent and efferent vessels between superficial and deep inguinal nodes and is complementary to LSG.

DISCUSSION

Summary of evidence

This systematic review evaluated the evidence for imaging and diagnostic modalities across four clinical domains: diagnostic accuracy, subclinical detection through prospective surveillance, anatomical assessment, and surgical planning. For diagnostic accuracy, NIRF-L and MRL demonstrated higher sensitivity for early or superficial lymphatic dysfunction compared with LSG, with MRL offering three-dimensional visualization of both superficial and deep collectors. For anatomical assessment, high-frequency US imaging is emerging as a cost-effective adjunct that enables real-time vessel characterization and preoperative mapping. LSG retains value for whole-limb physiologic assessment and remains the most widely available functional study in nuclear medicine departments. Table II summarizes the technical parameters for imaging and diagnostic modalities in lymphedema assessment.

Upper extremity evidence. Upper extremity lymphedema benefits from the most robust evidence base across all four clinical domains. For subclinical detection and prospective surveillance, RCT evidence from Ridner et al[16] (PREVENT trial) demonstrated a 59% relative risk reduction in chronic BCRL when BIS-triggered surveillance was coupled with early conservative intervention. Meta-analytic data from Shah et al,[34] incorporating more than 67,000 women, confirmed BIS superiority over circumferential monitoring, with annualized chronic BCRL incidence of 1.5% in BIS-monitored cohorts vs 7.7% with circumference monitoring. These findings represent the strongest available evidence for any diagnostic or imaging modality in lymphedema and

support BIS as the primary tool for subclinical detection in at-risk upper extremity populations.

For diagnostic accuracy, ICG lymphography demonstrated 100% diagnostic accuracy compared with 62% sensitivity for LSG in early-stage disease.[14] MRL demonstrated 92% to 100% sensitivity with 85% to 100% specificity for abnormal lymphatic vessels.[15] For anatomical assessment, UHFUS imaging at 70 MHz detected significantly more lymphatic vessels than conventional 18 MHz US imaging (sensitivity 94.9% vs 66.3%).[33] For surgical planning, Wiser et al[18] established that no single modality adequately represents the disease state. For treatment response, three RCTs[19-21] used imaging modalities including perometry, LSG, dielectric constant measurements, and ARFI elastography to evaluate therapeutic interventions, with LSG demonstrating dual utility as both diagnostic and therapeutic guidance tool for optimizing manual lymphatic drainage.

Lower extremity evidence. Lower extremity lymphedema evidence derives primarily from observational studies. MRL at 3.0 T achieved 100% sensitivity for lymph vessel abnormalities vs 79% for LSG ($\kappa = 0.93$ for delayed drainage), while LSG showed higher specificity for lymph node depiction (100% vs 78%).[26] Noncontrast T2-weighted MRI detected lymphangiectatic lesions in 97.5% of extremities,[23] and SPECT/CT added diagnostic information in 96.4% of cases beyond planar LSG.[22] US imaging differentiated dependent edema from lymphedema based on distinct echogenicity patterns.[25]

Two ICG-based classifications address lower extremity drainage: the SCaT[27] system tracks lymphatic redistribution with severity progression, while the Shinaoka[28] (LPad) classification links pathway defects to severity staging (AUC, 0.834 vs clinical model, 0.792; $P = .029$). For surgical planning, US imaging achieved 95.5% sensitivity and 92.9% specificity for vessel detection,[31] with cross-sectional height reliably differentiating ectasis from contraction types (AUC, 0.78),[30] and ICG lymphography enabled real-time LVA site selection.[32] Perometry and BIS demonstrated the greatest consistency for monitoring treatment response.[29]

Surgical planning implications

The evidence from this review supports the use of complementary modalities for surgical planning in both anatomical regions. For patients being evaluated for physiologic microsurgery including LVA and vascularized lymph node transfer of the upper extremity, studies have demonstrated that NIRF-L provides effective superficial lymphatic mapping while MRL offers deep-system evaluation, and their combined use may provide complementary information to improve anastomosis planning. High-frequency US imaging adds real-time vessel characterization and has shown feasibility for preoperative mapping in the upper arm. In addition, BIS assessment may identify patients with subclinical disease who could benefit from conservative management before surgical consideration.

For the lower extremity, the evidence supports the combined use of NIRF-L and high-frequency US imaging for superficial system assessment, with MRL providing particular value in complex cases or when deep system visualization including inguinal and pelvic nodes is required. Stress-based LSG provides functional transport information unavailable from anatomical imaging alone. Region-specific staging systems such as SCaT[27] and Shinaoka[28] have been shown to guide surgical target selection based on the location and severity of lymphatic pathway defects. Lower extremity surgical planning also requires consideration of longer examination times across all modalities and the need for additional injection sites compared with the upper extremity.

In resource-limited settings, the available evidence suggests that LSG combined with high-frequency US imaging may provide a practical evaluation approach for both upper and lower extremity lymphedema. The addition of ICG has been shown to significantly improve diagnostic sensitivity and surgical planning accuracy. MRL has demonstrated the highest anatomical detail but may be best used in complex cases or when available at low marginal cost.

Limitations

Heterogeneity in imaging protocols, staging systems, and outcome definitions limited quantitative meta-analysis. The majority of included diagnostic cohorts were single-center studies with small samples of 6 to 118 participants, reducing external validity. In addition, upper extremity evidence is heavily weighted toward BCRL, with limited data on primary or noncancer-related secondary lymphedema of the arm.

Quality assessment revealed consistent limitations across included studies, including paucity of data on sequence generation in older RCTs, inability to blind participants and personnel due to the nature of interventions, incomplete reporting of outcome data, selective outcome reporting, and unclear manufacturer funding disclosures, particularly for device studies. In addition, publication bias is a concern, as studies with favorable diagnostic performance are more likely to be published than negative or inconclusive findings. This may inflate reported sensitivity and specificity values across the literature. Selective outcome reporting was also observed. Several studies presented only statistically significant results or favorable subgroup analyses while omitting nonsignificant findings, which could overestimate the clinical utility of certain imaging modalities. In addition, diagnostic thresholds for BIS technology were predominantly developed by industry-affiliated groups, raising the possibility that commercially motivated reporting may have influenced the evidence base.

Implications for research

The findings of this systematic review highlight several priorities for future investigation. The most urgent unmet need is a prospective surveillance RCT for lower extremity lymphedema analogous to the PREVENT trial, as no comparable data currently exist to guide early detection strategies in this population. Development and validation of lower extremity-specific BIS diagnostic thresholds, bilateral upper extremity BIS protocols, and whole-body impedance mapping technology represent additional critical priorities. Multicenter prospective studies with standardized imaging protocols and outcome definitions are needed to strengthen the evidence base across all four clinical domains evaluated in this review.

CONCLUSIONS

This systematic review evaluated imaging and diagnostic modalities across four clinical domains: diagnostic accuracy, subclinical detection through prospective surveillance, anatomical assessment, and surgical planning. RCT evidence supports BIS-triggered prospective surveillance for upper extremity lymphedema, with the PREVENT trial demonstrating a significant reduction in chronic BCRL progression. NIRF-L and MRL provide complementary diagnostic and surgical planning information across both extremities, while region-specific ICG-based classification systems address the unique anatomical drainage patterns of the lower extremity. LSG remains essential for baseline functional assessment. However, lower extremity lymphedema lacks equivalent prospective trial data, representing a critical evidence gap. Anatomically tailored imaging protocols and region-specific staging systems are necessary for both upper and lower extremity lymphedema, and multicenter RCTs addressing lower extremity surveillance and emerging technologies are urgently warranted.

AUTHOR CONTRIBUTIONS

Conception and design: TO, AO
Analysis and interpretation: SL, AI, NT, AO
Data collection: SL, CP, AI, BR, JM, SC, NS
Writing the article: SL, CP, AI, BR, SC, NS
Critical revision of the article: SL, JM, TO, NT, AO
Final approval of the article: SL, CP, AI, BR, JM, SC, NS, TO, NT, AO
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: AO

FUNDING

None.

DISCLOSURES

None.

DATA AVAILABILITY

A protocol for this review was prepared and available via PROSPERO.

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Submitted May 19, 2026; accepted Jul 26, 2026.

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